REVIEW ARTICLE

# Aneurysms of the Ascending Aorta

Daniel Lavall, Hans-Joachim Schäfers, Michael Böhm, Ulrich Laufs


## SUMMARY

Background: Aneurysms of the ascending aorta present a special challenge to primary care physicians, internists, and cardiac surgeons because they remain asymptomatic until they present with either dissection or rupture.

Method: This review article is based on a selective search of the literature.

Results: In the elderly, aneurysms of the ascending aorta are mainly caused by atherosclerosis. In younger patients, the most common cause is Marfan syndrome; less commonly, younger patients may have Loeys-Dietz syndrome, non-syndromic familial aortic aneurysms, or aortic valve malformations. Genetic variants predisposing to the development of sporadic aortic aneurysms have recently been identified. The risk of rupture and dissection depends on the aortic diameter: when the diameter exceeds 55 mm, surgery improves the outcome, as the risk of surgical complications is lower than the mortality due to rupture or dissection. A more accurate prognosis can be obtained by normalizing the aortic diameter to the body surface area. For patients with Marfan syndrome or a bicuspid aortic valve, the indications for surgery should be determined on an individual basis, depending on additional risk factors. Randomized treatment trials are lacking. The medical management of aneurysms of the ascending aorta consists of monitoring the size of the aneurysm, controlling blood pressure, and treating any cardiovascular risk factors. Patients with Marfan syndrome benefit from preventive treatment with beta-blockers. Advances in the pathophysiological understanding of aortic aneurysms have led to the testing of new types of treatment, e.g., with AT1 antagonists.

Conclusion: With the aid of a risk-based treatment strategy, surgery can be properly timed to prevent dissection, which is usually lethal when it occurs. More research is needed on the pathogenesis of this condition so that better preventive treatments can be developed.



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An aneurysm is a dilatation of a blood vessel to more than 150% of the diameter expected for sex, age, and body weight; lesser dilatations are called ectasia (1). Depending on age, aortic aneurysms are the 17th most common cause of death in the USA. The real number is likely to be higher, because of the number of unknown fatal dissections and ruptures (2, e1). The incidence of thoracic aortic aneurysms is about 5 to 10 per 100 000 patient years, with a peak incidence during the sixth and seventh decades of life (e2, e3). Men are two to four times more frequently affected than women. Aortic dissection is diagnosed later in women; that is, the delay from onset of symptoms to diagnosis is longer than in male patients (6.40 hours in women compared to 3.94 hours in men) (e4).

Recent genome-wide association studies (3) and molecular biological studies (4, e5, e6) have improved our understanding of the pathogenesis, and on this basis new therapeutic options are being tried. One example is the importance of transforming growth factor β (TGF-β) for the pathogenesis of aneurysms in Marfan syndrome (4, e5, e6). The recent studies show that, in addition to maximum aortic diameter, there exist patient characteristics and specific risk factors for aortic complications that enable improved individual risk prediction and carefully targeted selection of patients for surgical aortic replacement (2, 5).

## Anatomy

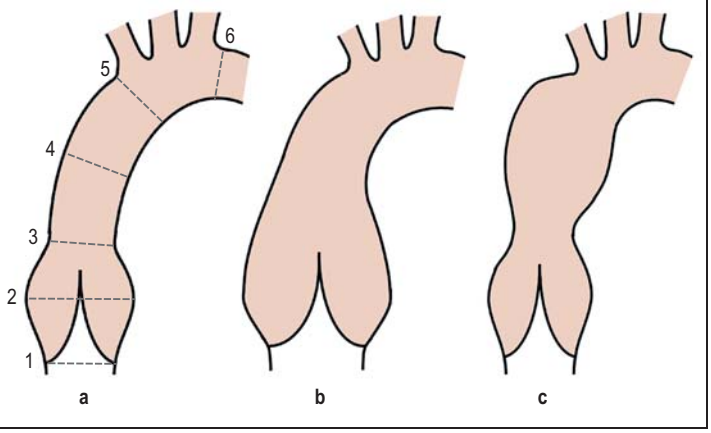
The ascending aorta consists of the aortic root and a tubular segment; the border between the two is called the sinotubular junction (*Figure 1a*). The aortic root corresponds to the area of vertical expansion of the aortic valve, the geometry of which is essential to the function of the aortic valve. Diseases of the ascending aorta are the most common reason for aortic valve regurgitation (6, e7), especially when the sinotubular junction is involved (e8).

## Etiology and pathophysiology

### Atherosclerosis

Atherosclerosis is the most common cause of aortic aneurysms (*Table 1*). The incidence of aortic aneurysms correlates with hypertension, cigarette smoking, and advanced age (e6). Despite the association between atherosclerosis and aneurysms of the ascending aorta, little is known about the specific pathogenesis (1). An important factor is increased activity of matrix metalloproteinases, which regulate tissue homeostasis (7, e9, e10).

**FIGURE 1**




**Configuration of aortic root and ascending aorta, with measuring points (1–6) for assessing aortic diameter**

a) Normal configuration, b) typical aortic root dilatation in Marfan syndrome patients, c) aneurysm in the tubular part of the ascending aorta.
Measuring points: 1 = aortic annulus, 2 = sinus of Valsalva, 3 = sinotubular junction, 4 = middle of ascending aorta, 5 = beginning of the aortic arch, 6 = end of the aortic arch

### Connective tissue disorders: Marfan syndrome and Loeys–Dietz syndrome

Marfan syndrome is a connective tissue disorder caused by a mutation of the fibrillin-1 gene (8). The prevalence of Marfan syndrome is around 1:3000; many patients remain undiagnosed (e11). The 2010 revised diagnostic criteria for Marfan syndrome (Ghent nosology) take account of the variable phenotype by simplifying the diagnostic criteria (e12). The emphasis is on aortic disease (aortic aneurysm, aortic dissection, rupture), which almost all patients with Marfan syndrome develop in the course of life. This leads to a reduced life expectancy: around 32 years without treatment and up to 60 years with optimal treatment (1, 9). Aortic aneurysms occur predominantly in the aortic root area (*Figure 1b*). If the sinotubular junction is involved, aortic valve regurgitation is often present (15% to 44%) (8).

Loeys–Dietz syndrome is an autosomal dominant genetic aortic aneurysm syndrome caused by a mutation of the TGF-β receptor. The more common phenotype, phenotype 1, is characterized by tortuosity (84%) and aneurysms (98%) of the great vessels, hypertelorism (90%), and bifid uvula or cleft palate (90%). The second phenotype resembles the vascular Ehlers–Danlos syndrome, a connective tissue disorder in which collagen III synthesis is impaired, leading to arterial dissections and ruptures (65%) and rupture of hollow organs (21%) (e13). Because type 2 Loeys–Dietz syndrome has a more aggressive course in terms of aortic aneurysms, but a lower operative mortality associated with aortic replacement (4.8% compared to 45% in vascular Ehlers–Danlos syndrome), distinguishing the genotypes is relevant to management decision making. The mean life expectancy of patients with Loeys–Dietz syndrome is 37 years, because aortic dissections occur at a younger age (26.7 years) and at smaller diameters (from 40 mm) (10).

The cause of the vascular wall instability in Marfan and Loeys–Dietz syndrome is increased TGF-β activity (8, 10). In a mouse model molecular signaling pathways were identified through which TGF-β antibodies and angiotensin-II-receptor type 1 (AT1) antagonists can inhibit aneurysm growth (4, e5, e6). However, it cannot be automatically assumed that these mechanisms operate similarly in other aneurysm entities, because mechanisms of development vary (11).

### Familial aortic aneurysms and genetic risk factors

Familial aggregations of aortic aneurysms and aortic dissection in the absence of a syndrome or connective tissue disease are also seen. These are caused by various genetic mutations (MYH11, ACTA2); at present the details of the mechanisms are only known in part (1). In a recent genome-wide association study, a genetic variant (15q21.1) was identified that is associated with sporadic thoracic aortic aneurysm. This gene codes for fibrillin-1, indicating parallels in the pathogenesis of sporadic aortic aneurysms and Marfan syndrome (3).

### Erdheim–Gsell media degeneration

The histopathology of aortic aneurysms was described by Gsell and Erdheim in 1928/1930 as "cystic medial necrosis," consisting of necrosis of smooth vascular muscle cells, destruction of elastic fibers, and proliferation of basophilic ground substance in the cell-free areas (12). Since neither cysts nor necrosis appear consistently, today the term "media degeneration" seems more appropriate (7). This degeneration leads to deterioration of the vascular mechanics of the aorta, with aortic distensibility decreasing as its diameter increases, and wall stress rising in dependence on blood pressure, in accordance with Laplace's law (e14).

### Congenital disorders of the aortic valve

The bicuspid aortic valve syndrome involves not only the aortic valve but also the ascending aorta, visible in histopathologic changes (7). One underlying mechanism is reduced expression of endothelial nitric oxide synthase (13, e15). Around 26% of patients with a bicuspid aortic valve develop an aneurysm of the ascending aorta. So long as elective surgical aortic replacement is carried out early enough, the incidence of aortic dissection is low at 3.1% per 10 000 patient years—but that is eight times higher than in the general population (14). In a bicuspid aortic valve, the valve anatomy gives rise to altered hemodynamics, independently of valve function, with turbulent eccentric flow acceleration in the ascending aorta (15). On the basis of this, a combined development mechanism is likely, with predisposing congenital aortopathy and altered hemodynamics in the ascending aorta (14).

By contrast, the poststenotic turbulences in acquired (tricuspid) aortic valve stenosis appear to play a smaller

**TABLE 1**

**Causes and pathophysiology of aneurysms of the ascending aorta, in descending order of prevalence**

| Cause | Pathophysiology | Number of patients with aneurysms as a percentage of those with the underlying disease |
|---|---|---|
| Degeneration | Atherosclerosis, hypertension, smoking, age<br>Exact mechanisms only partially understood, increased activity of MMP-2 and MMP-9 | ~ 4.6% of over 60-year-olds (e26) |
| Connective tissue disorder<br>– Marfan syndrome<br>– Loeys–Dietz syndrome | Instability of the extracellular matrix<br>– Fibrillin-1 mutation<br>– TGF-β-receptor mutation | <br>~ 75% (e23)<br>~ 98–100% (10) |
| Congenital anomalies of the aortic valve<br>– Bicuspid aortic valve<br>– Unicuspid aortic valve<br>– Turner syndrome | Congenital aortopathy and altered hemodynamics in the ascending aorta due to altered aortic valve morphology; media degeneration | <br>~ 26% (14)<br>~ 23% (16)<br>~ 33% (17) |
| Genetic causes<br>– Familial aortic aneurysms (non-syndrome)<br>– Genetic variants | Gene mutations<br>– Coding for the contractile function of smooth vascular muscle cells (MYH11, ACTA2) or the TGF-β receptor (TGBR2)<br>– 15q21.1 polymorphism, encoding fibrillin-1 | <br>4–14% (1)<br><br>Unknown |
| Aortitis | Postinflammatory aortic root dilatation after inflammatory changes to the aortic wall | 30–67% (18) |

MMP: matrix metalloproteinases; TGF-β: transforming growth factor β; MYH11: smooth muscle specific beta-myosin heavy chain; ACTA2: actin, alpha 2, smooth muscle aorta; TGFBR2: transforming growth factor β receptor type 2

**TABLE 2**

**Sex-specific mean dimensions of the aortic root**

| Structure | Diameter (cm), men | Diameter (cm), women | p value | Index (cm/m$^2$), men | Index (cm/m$^2$), women | p value |
|---|---|---|---|---|---|---|
| Annulus | 2.6 ± 0.3 | 2.3 ± 0.2 | <0.001 | 1.3 ± 0.2 | 1.3 ± 0.2 | ns |
| Sinus of Valsalva | 3.4 ± 0.3 | 3.0 ± 0.3 | <0.001 | 1.7 ± 0.2 | 1.8 ± 0.2 | ns |
| Sinotubular junction | 2.9 ± 0.3 | 2.6 ± 0.3 | <0.001 | 1.5 ± 0.2 | 1.5 ± 0.2 | ns |
| Prox. ascending aorta | 3.0 ± 0.4 | 2.7 ± 0.4 | <0.001 | 1.5 ± 0.2 | 1.6 ± 0.3 | ns |

Mean values for two-dimensional echocardiography in adults. Men show larger absolute aortic diameters than women, but after indexing (relating aortic diameter to body surface area) the difference is no longer significant. Calculation of body surface area according to Dubois: body surface area (m$^2$) = 0.20247 × body height (m)$^{0.725}$ × body weight (kg)$^{0.425}$; Index (cm/m$^2$) = diameter (cm) / body surface area (m$^2$). Sample calculation: man, 70 kg, 180 cm: body surface area: 1.89 m$^2$.
ns: not significant; prox.: proximal.
From Roman MJ, et al.: Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989; 64: 507–12 (24); reproduced by kind permission of Elsevier, Oxford, UK

part in the development of aneurysms than was hitherto assumed, since this association rarely occurs in older patients despite a high prevalence of aortic valve stenosis (6).

The rare unicuspid aortic valve has many characteristics in common with the bicuspid valve, with valve dysfunction and aortic aneurysms occurring early in life (16).

About 75% of patients with Turner syndrome show cardiovascular anomalies, and 20% of these are a bicuspid aortic valve. Because of their smaller stature it should be noted that, although the ascending aortic diameter is normal in absolute terms, after indexation for body size one in four patients with Turner syndrome has a dilated aorta (*Table 2*). There is an increased risk of dissection, especially if other risk factors such as corrected or uncorrected aortic coarctation is present as an expression of a relevant aortopathy or arterial hypertension (17).

### Aortitis

Aortitis is rarely the cause of an aortic aneurysm. In patients with manifest aortitis, however, postinflammatory dilatation of the aortic root and aortic valve regurgitation is common. Syphilitic aortitis is a rare occurrence today and should only be considered as a diagnosis when syphilis is suspected on clinical grounds. The differential diagnosis should include

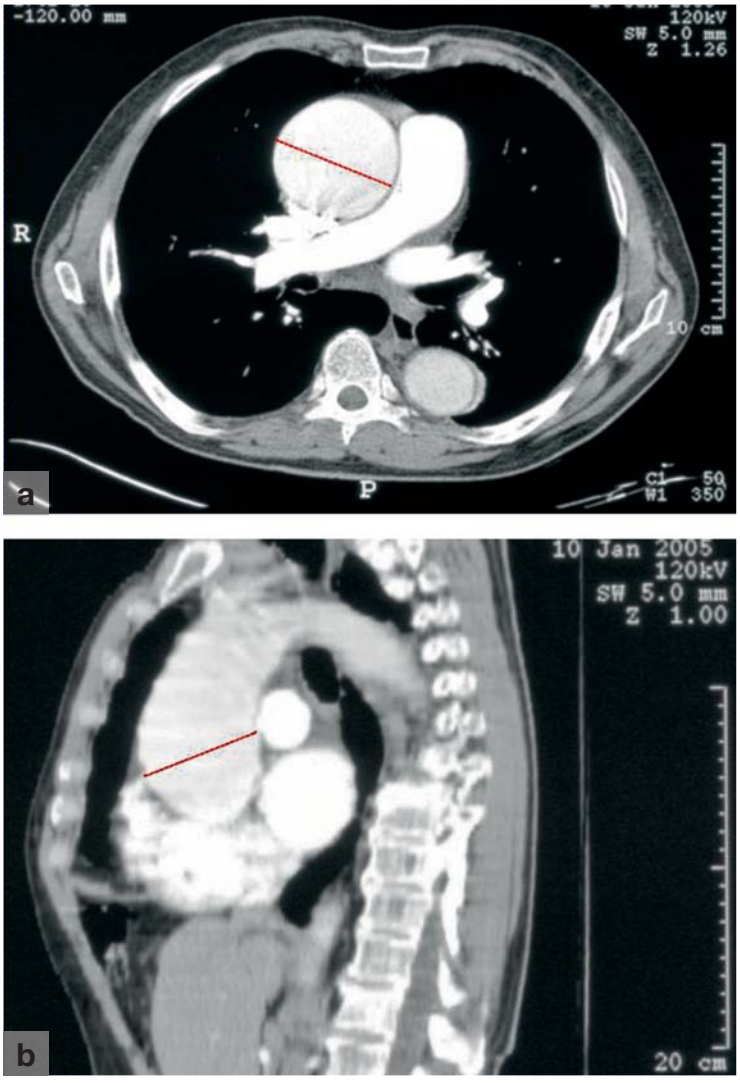



**Figure 2: Measuring aortic diameter on computed tomography**

a) Incorrect measurement of the aorta in a section that is oblique to the axial plane

b) Correct measurement in the sagittal plane, perpendicular to the direction of blood flow

**TABLE 3**

**Recommended indications for elective surgical replacement of the aorta**

| Indication | Class of recommendation | Level of evidence |
|---|---|---|
| ≥ 50 mm for patients with Marfan syndrome*1 | I | C |
| ≥ 45 mm for patients with Marfan syndrome and risk factor*2 | IIa | C |
| ≥ 50 mm for patients with bicuspid valve and risk factor | IIa | C |
| ≥ 55 mm for all other patients | IIa | C |

The recommendations are valid irrespective of the severity of any concomitant aortic valve regurgitation.

*1 Patients with connective tissue disorders, Turner syndrome, and marfanoid patients who do not fulfill the Marfan criteria, are treated as Marfan patients.

*2 The presence of at least one risk factor suffices for risk stratification. The following are risk factors: familial predisposition to aortic dissection, aneurysm growth rate >5 mm/year, aortic valve morphology (unicuspid, bicuspid), corrected or uncorrected aortic coarctation, intention to have children (female patients with Marfan and Loeys–Dietz syndrome). Updated recommendations based on (6)

Takayasu aortitis in female patients younger than 40 years and giant cell aortitis in patients older than 75 years (18).

## Diagnosis and risk assessment

### Diagnosis

The decisive element in diagnosing an aneurysm is the greatest vascular diameter. Transthoracic echocardiography is the method of choice for screening and monitoring. Since in most cases only the aortic root and proximal ascending aorta can be assessed (1, 2, 7), in cases where echocardiography shows a dilated aorta, or where visualization is poor, computed tomography or magnetic resonance imaging should be carried out (6). Computed tomography offers extensive reconstruction options, although in younger patients the cumulative radiation dose from repeat examinations should be borne in mind (e16). Magnetic resonance imaging is not available everywhere and may be contraindicated in patients with claustrophobia. Transesophageal echocardiography allows good visualization of the ascending aorta but is stressful for the patient and associated with (small) risks.

Monitoring of size progression requires reproducible measurement of the dilated vascular segment (*Figure 1a*) (2):

- Aortic annulus
- Sinus of Valsalva
- Sinotubular junction
- Middle of the ascending aorta
- Beginning and end of the aortic arch.

The diameter is determined in a plane perpendicular to the blood flow; for this reason axial cross-sections are usually inappropriate and multidimensional reconstructions are needed (*Figure 2*).

### Complications

Stanford type A aortic dissection (dissection of the ascending aorta with or without involvement of distal segments) is associated with a high mortality whether it is treated conservatively or by emergency surgery (19); the risk of dying preoperatively rises by 1% to 2% every hour. Even when the patient is transferred without delay to a heart surgery center, he or she has a 10% to 15% risk of dying under surgery.

The rationale for elective replacement of the ascending aorta is to prevent aortic complications (1). Elective aortic replacement in Marfan patients improves the prognosis decisively compared to emergency surgery when Stanford A aortic dissection has occurred (30-day mortality 1.5% vs. 11.7%). If the perioperative phase is survived, there is no difference in long-term prognosis (23 years) (20).

From an aortic diameter of 40 mm and upwards, maximum aneurysm size correlates directly with mortality from aortic rupture and dissection (2, e17). At diameters greater than 60 mm the annual rupture and dissection rate is around 6.9% and mortality 11.8%. This corresponds to a doubling of the complication rate compared with an aortic diameter of 50 to 59 mm.

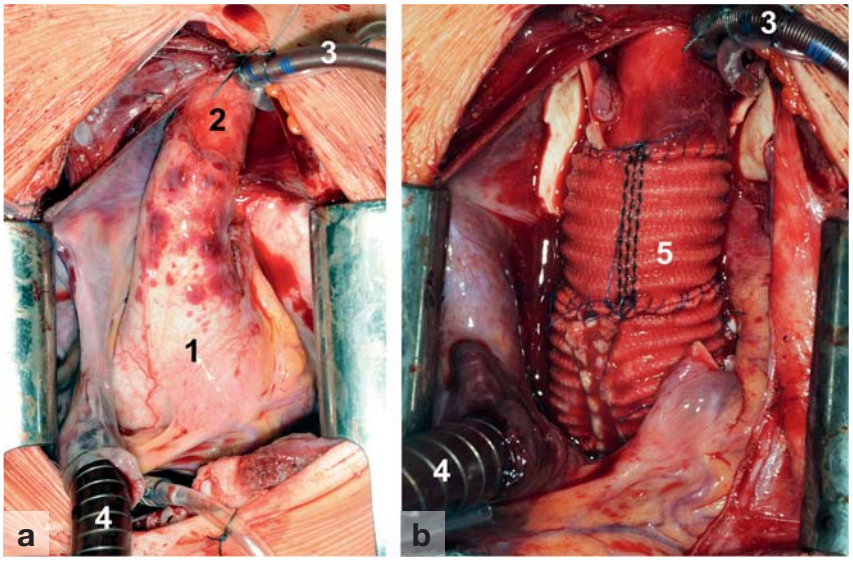



**Figure 3:**
Operative site in a patient with an aneurysm of the ascending aorta
a) Prepared aneurysm of the ascending aorta approached through a median sternotomy.
b) After aneurysm resection and graft implantation.
1 = aneurysm of the proximal ascending aorta
2 = non-aneurysmal distal ascending aorta
3 = arterial cannula (aorta)
4 = venous cannula (right atrium) of the extracorporeal circulation
5 = implanted aortic graft after aneurysm resection

Where aortic diameters are smaller, the increase in complications (10% to 25% per 10 mm) is lower (2, 6).

#### Individual risk assessment

Since aortic diameter increases with age, body weight, and body height (21), it is difficult to provide generally defined absolute normal values for the ascending aorta. Instead of individual normal values, therefore, ratios have been developed that relate aortic diameter to body weight and height (17, 22, 23). Despite a paucity of study evidence, this appears plausible and practical from a clinical point of view (*Table 2*) (24). Especially in women and patients of small stature (body surface area [as a measure of body size] ≤1.68 $m^2$), e.g., in Turner syndrome, the risk of complications can be underestimated on the basis of absolute values (6, 17, e18). In patients with Turner syndrome, aortic dilatation is present when the maximum aortic diameter is greater than 2.0 $cm/m^2$, and at ≥2.5 $cm/m^2$ there is a high risk of aortic dissection (17). Index threshold values for general surgical indication have not yet been established, since existing studies used absolute values.

Individual management decisions are governed by, in addition to aortic diameter, the presence of other specific risk factors (2, 5) (*Table 3*):

- A familial predisposition to aortic complications
- Growth rate (>5 mm/year)
- Aortic valve morphology (unicuspid, bicuspid)
- Corrected or uncorrected aortic coarctation
- Intention to have children (in women with Marfan or Loeys–Dietz syndrome).

## Conservative and surgical treatment

There are no large randomized controlled studies on the treatment of aortic ascending aneurysms. Recommendations (1, 6) are based on small cohort studies and observation studies, corresponding to evidence grade B or C (*Table 3*).

#### Medical therapy

The aim of medical therapy is to reduce wall stress in the aneurysmal aorta. Specific therapies attempt to influence the pathophysiologic changes in aortic aneurysms (11). Because of the significance of atherosclerosis, minimizing cardiovascular risk factors is obligatory. Blood pressure must be controlled: In patients with diabetes mellitus it should be less than 140/90 mm Hg, in patients with renal insufficiency lower than 130/80 mm Hg. Moderate physical activity probably acts preventively against the progression of atherosclerosis-related aneurysms. To prevent blood pressure spikes, competitive sports should be avoided by patients with an aortic diameter greater than 40 mm (5, e19). The restriction of physical activity remains a decision to be made on case-by-case basis, since insufficient study data are available. Beta-blockers reduce the wall stress in the aneurysm by reducing blood pressure and through their negative inotropic effect (11). In Marfan patients, prophylactic beta-blockade with propranolol reduces the progression of the aortic dilatation and the occurrence of complications, and it is therefore recommended in these patients (1, 6). For aortic disease of other etiologies, there is no evidence of a specific benefit from beta-blockers. For angiotensin-converting enzyme inhibitors and AT1-antagonists, existing data are contradictory (11). In Marfan patients, losartan reduced aortic root dilatation, but no prospective controlled studies have yet been performed (4). Statins are indicated in cardiovascular primary and secondary prevention, but so far no specific studies have been published on additional benefit in aortic aneurysms (11).

#### Frequency of diagnostic examination

On the important practical question of how often diagnostic examinations should be carried out in patients with known aortic dilatation, no reliable study data

exist. In our opinion, the first follow-up imaging should be carried out 6 months after the diagnosis is made in order to assess the rate of growth of the aneurysm. If the size has remained stable, further follow-up imaging at yearly intervals is recommended. If findings remain constant for 2 to 3 years, the follow-up examinations can be spaced out at 2- to 3-year intervals. On the other hand, patients at high risk, e.g., those with a familial predisposition to aortic dissection, those with rapid enlarging aneurysms, and patients with Loeys–Dietz syndrome, should be followed up every 3 to 6 months (1). Regular doctor visits and screening are important for first-degree relatives because of the familial risk.

#### New intervention criteria

There are no specific symptoms of a chronic aneurysm of the ascending aorta. Acute aortic dissection should be included in the differential diagnosis of patients with sudden onset of chest or back pain, syncope, stroke, or acute heart failure. However, these symptoms are not typical of chronic aneurysm without dissection.

Study results in the past few years show that, in addition to the diameter, the dissection risk is largely determined by patient characteristics and specific risk factors. For this reason, we recommend carefully targeted selection of patients for surgery (*Table 3*). Marfan patients with risk factors should undergo elective surgery with an aneurysm diameter of ≥45 mm, and those without risk factors when their aneurysm diameter is ≥50 mm. A similar stepped approach is recommended for patients with bicuspid aortic valve: with risk factors, surgery should be performed at a diameter of ≥50 mm, whereas without risk factors the threshold is the same as for those with a tricuspid aortic valve, i.e., ≥55 mm. Patients with aortic dilatation as part of another genetic syndrome, e.g., Turner syndrome, or marfanoid patients who do not fulfill the Marfan criteria, should be treated as Marfan patients because of their risk profile. In patients with Loeys–Dietz syndrome, the progressive dilatation with high risk of complications may justify a more aggressive approach (surgery when aneurysm diameter is ≥40 mm). If aortic valve surgery is indicated, replacement of the aorta in the same session may be considered for patients with an aneurysm diameter of ≥45 mm. The treatment decision should take account of co-morbidities, age, life expectancy, and the condition of the wall found intraoperatively (6).

Patients with genetic aortic aneurysm syndromes should be managed at an experienced center with cardiology and heart surgery facilities, where the operative risk is lower (1, 5–7, e20, e21).

#### Surgical treatment

The surgical mortality risk associated with aortic replacement lies between 1% in young patients and >5% in older patients, depending on whether the aortic valve is replaced at the same time, and on the experience of the surgeon and the patient's co-morbidities (e20, e22).

Surgical correction (*Figure 3*) is guided by the aneurysm location. Distal to the sinotubular junction, implantation of a tube graft suffices. If the aneurysm involves the aortic root, aortic regurgitation is often present. For combined aortic valve and ascending aorta replacement, either the valve and the aortic prostheses can be implanted sequentially or a composite graft can be placed. The composite graft consists of a mechanical aortic valve integrated into the tube graft. Surgical implantation is straightforward, but the coronary ostia have to be reimplanted. In addition, lifelong anticoagulation is required. Long-term studies after aortic valve replacement (biological or mechanical) show a complication risk for reoperation, endocarditis, thromboembolism, and bleeding of 3% to 3.5% per year (e23). Life expectancy after aortic valve surgery depends on the age of the patient and on the following (e24):

- Left ventricular ejection fraction
- Coronary heart disease
- Kidney failure
- Diabetes mellitus
- Liver and lung disease.

On average, the probability of survival is 79% after 10 years and 53% after 20 years (e25). In experienced centers, reconstruction of failing aortic valves seems to show the lowest rates of valve-associated complications, especially in younger patients (1, 5). Reconstruction of bicuspid aortic valves with good results is also possible (25).

**KEY MESSAGES**

- When an aneurysm of the ascending aorta is present or suspected to be present, diagnostic imaging of the aorta should be carried out, using transthoracic echocardiography in the first instance.
- Medical therapy consists of rigorous secondary prevention of cardiovascular disease, especially careful control of blood pressure. In patients with Marfan syndrome, prophylactic beta-blocker therapy is indicated.
- Patients with an aortic diameter >40 mm should reduce physical activity to a moderate level in order to avoid blood pressure spikes, and should avoid competitive sports.
- Regular imaging follow-up is needed so as not to overshoot the right moment for surgery.
- Selection of patients for surgery is largely based on patient characteristics and specific risk factors, in addition to aortic diameter (*Table 3*).

**Conflict of interest statement**
The authors declare that no conflict of interest exists.

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